Diabetologia (1996) 39: ■-■

APRIL

Diabetologia

Letter to the editor

Vaccines modulate IDDM

Dear Sir,

Dahlquist and Gothefors [1] recently published Swedish cohort data examining the effect of administering BCG vaccines at birth. Our analysis of their data indicates that immunization at birth caused both a clinically and statistically significant reduction in diabetes mellitus. Our primary concern with the authors' analysis is that it fails to acknowledge that the smallpox vaccine was discontinued in 1976 in Sweden, while the BCG vaccine was discontinued in 1975. The smallpox vaccine was administered in Sweden primarily at 2 months or 9 months of age as compared to the BCG vaccine being administered at birth. Our data (patent application PCT/US 94/08825) from non-obese diabetic (NOD) mice and human ecological studies show that vaccines administered starting after 2 months of life increase the incidence of diabetes thus having the opposite effect of administering vaccines at birth. The Swedish data need to be analysed in a way to compensate for the confounding effect of the smallpox vaccine.

Swedish law until early 1976 required immunization with smallpox vaccine prior to the age of 5 years. Unfortunately good records on the acceptance rates in the birth cohorts are not available. Swedish public health officials have indicated that the smallpox vaccine was being increasingly withheld in anticipation of the discontinuation of the law, as it became apparent to physicians that the risk of children developing adverse responses to immunization exceeded the risk of being infected with smallpox. Data from the Netherlands showed this trend clearly. In the Netherlands the smallpox vaccine was given around 9 month of age and was mandatory by age 1 year before the law was repealed on 28 November 1975. The acceptance rates by age 1 year in the Dutch birth cohorts of 1970–1975 were 88 %, 87 %, 82 %, 66 %, 47 %, and 9 % respectively.

Table 1 analyses the differences between the birth cohorts that received BCG, 1973–1974, and those that did not, 1976–1977. Dahlquist and Gothefors' analysis [1] which ignores the effect of the smallpox vaccine is listed as assumption A. Three additional assumptions were included which refrain from comparing the 1973 to the 1977 cohort because the variation in acceptance rate of the smallpox vaccine between these cohorts is the greatest. The administration of BCG at birth is associated with a drop in the cumulative incidence of diabetes by 32–49 cases of diabetes/100,000 individuals. The most appropriate way to compensate for the confounding effect of the smallpox vaccine would be to compare the 1974 and 1976 cohorts, which show a difference of 48.64 cases/100,000. This data is consistent with ecological data from western Europe looking at published incidence of diabetes in 0–15-year-olds in a group of countries where the BCG vaccine is given at birth (Republic of Ireland, France, Austria, Switzerland, Portugal) and comparing this to the incidence of diabetes in a group of countries which have similar immunization schedule but lacking BCG (Iceland, Netherlands, Spain, Belgium, Luxembourg). The mean annual incidence of diabetes in the two groups was 7.4 cases/100,000 (range 6.8–7.8) and 10.92 cases/100,000 (range 9.8–12.4), respectively. The cumulative effect of administering a BCG vaccine at birth according to this ecological data is 52.8 cases/100,000 (3.52 × 15 years).

These data are consistent with our findings that administration of a vaccine starting after 2 months of age results in an increased incidence of diabetes. A higher acceptance rate with the smallpox vaccine can explain the higher incidence of diabetes in the 1973 vs 1974 cohorts. While not presenting the data, Dahlquist and Gothefors state that the pertussis vaccine had no effect on the development of diabetes in Sweden. Extrapolation of this report to other pertussis vaccines would be inappropriate since the Swedish pertussis vaccine had little biological activity in regards to protecting against pertussis, efficacy was calculated at 9 %, and lacked an aluminium adjuvant common in many ■■■ (DTP) vaccines. Only three doses of the pertussis vaccine were given in Sweden compared to five in the USA. It has been shown that different brands of pertussis vaccines vary in their ability to induce antibodies capable of binding human heat shock proteins. Another reason why Dahlquist's data may differ from our data is that the Swedish control group was likely to have developed pertussis since the disease was endemic in Sweden. We studied the effect of the pertussis vaccine in areas where the incidence of pertussis had been greatly reduced by earlier immunization programmes and the control subjects were protected by herd immunity. Studying the effect of a vaccine on diabetes without ensuring that the control subjects are free of the infection will bias the results, because the natural infection may be as diabetogenic as the vaccine, making the vaccine appear to be safe. This conclusion

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Table 1. Analysis of Swedish insulin-dependent diabetes cohort study: the affect of the BCG and smallpox vaccines

Birth cohort	Cases of diabetes	Cohort size	Cumulative incidence/ 100,000	Mean		P value · Normal approximation Poisson distribution	
				incidence/ 100,000	Difference/ 100,000	1 Tail	2 Tail
1973	345	107,582	320.69				
				311.72			
1974	329	108,671	302.75				
					32.22	0.0363	0.0726
1976	342	97,327	351.39				
				343.94			
1977	320	95,098	336.49				
Assumption B: compare last cohorts							
1974	329	108,671	302.75	302.75			
					41.19	0.0097	0.0194
1976	342	97,327	351.39				
				343.94			
1977	320	95,098	336.49				
Assumption C: compare middle cohorts							
1974	329	108,671	302.75				
					48.64	0.0028	0.0057
1976	342	97,327	351.39				
Assumption D: compare first three cohorts							
1973	345	107,582	320.69				
				311.72			
1974	329	108,671	302.75				
					39.67	0.0133	0.0265
1976	342	97,327	351.39	351.39			
Assumptions A–D					Average 40.43		
Assumptions B–D					43.17		

is misleading and potentially harmful because differences in vaccination scheduling and formulation have been shown to greatly reduce the development of diabetes in animals.

The ability of a vaccine to determine the outcome of 50 cases of insulin-dependent diabetes/100,000 people is clinically very significant, representing 25 % of all cases of insulin-dependent diabetes in many countries. Fifty cases of severe morbidity/100,000 people has caused major changes in immunization practices previously. An international effort has been ongoing for some time to develop an acellular pertussis vaccine because the risk of permanent central nervous system sequela following the administration of the whole-cell pertussis vaccine is estimated at 0.2 cases/100,000 doses of vaccine administered. The *Haemophilus influenza* vaccine is being promoted for the prevention of *H. meningitis*, a condition that affects 100 in every 100,000 children in the USA. Assuming the *H. influenza* vaccines are 90 % effective and three doses are given, on average each dose prevents 30 cases/100,000 children immunized. We believe the affects of vaccines on diabetes are of tremendous clinical importance and that trials need to be started immediately to address the affect of vaccines on diabetes and other autoimmune diseases. We hope Dahlquist and Gothefors will reanalyse their data by including the 1975 cohort and later cohorts if possible.

Yours sincerely,
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References

1. Dahlquist G, Gothefors L (1995) The cumulative incidence of childhood diabetes mellitus in Sweden unaffected by BCG vaccination. Diabetologia 38: 874